CME-accredited Webinar:
The Identification and Diagnosis of Lennox-Gastaut Syndrome (LGS)

Ali A. Asadi-Pooya, MD

Shiraz University of Medical Sciences, Iran

Thomas Jefferson University, USA

Adam Strzelczyk, MD, MHBA, FEAN

Goethe-University Frankfurt, Germany

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Session Overview

1. Introduction to LGS
2. Definition of LGS
3. Diagnosis
4. Epidemiology
5. Aetiology
6. History of the characterisation and treatment of LGS
7. Treatment algorithm
8. Seizure emergency plan
9. Epidemiology and mortality in LGS

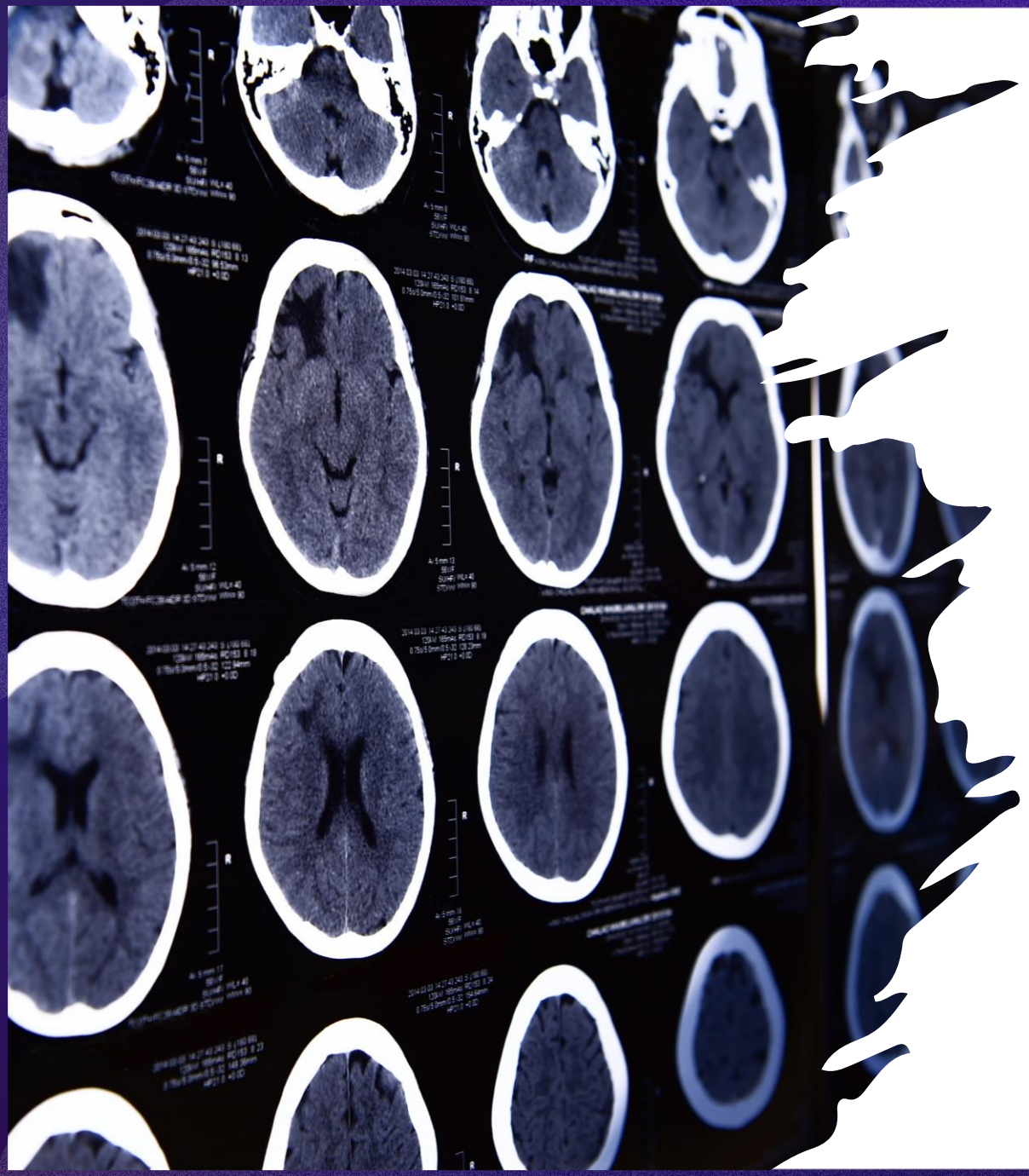
Introduction to Lennox-Gastaut syndrome

Ali A. Asadi-Pooya, MD

Professor of Epileptology

Shiraz University of Medical Sciences, Iran

Thomas Jefferson University, USA



What is Lennox-Gastaut Syndrome (LGS)?

Lennox-Gastaut syndrome (LGS) is a severe drug-resistant developmental and epileptic encephalopathy.

Definition

Traditional Definition (Triad of):

- Multiple drug-resistant seizure types; At least two types of seizures
- Cognitive and behavioural abnormalities, which may not be present at seizure onset
- EEG: generalised slow spike-waves and/or generalised paroxysmal fast activity

The ILAE Definition (Triad of):

- Multiple types of drug-resistant seizures with **onset prior to 18 years** (**one of which must include tonic**)
- Cognitive and often behavioural impairments, which may not be present at seizure onset
- EEG: Diffuse slow spike-and-waves **and** generalised paroxysmal fast activity

EEG: Electroencephalogram; ILAE: International League Against Epilepsy

Asadi-Pooya AA. Neurol Sci. 2018;39(3):403-414.
Specchio N et al. Epilepsia. 2022;63(6):1398-1442.

Diagnosis

The diagnosis of LGS is electro-clinical:

- A detailed clinical history: Age at onset, seizure types, cognitive and behavioral abnormalities
- An EEG

Traditional vs. New Definition

- In one study, all patients with an electro-clinical diagnosis of LGS (based on its traditional definition) at the outpatient epilepsy clinic at Shiraz University of Medical Sciences, Shiraz, Iran were included (from 2008 until 2020).
- In total, 3737 patients were registered in the database.
- Patients were reclassified based on the new definition of LGS.
- Based on its traditional definition, 300 patients (8%) were diagnosed as having LGS.
- According to the new definition of LGS, only 96 patients (32% of the traditional cohort and 2.6% of the whole cohort) had LGS.
- One patient, who had other criteria, had an age at onset of 21 years.
- 111 patients (37%) did not report having tonic seizures.
- 29 patients (9.7%) did not have SSW in their EEGs; 139 people (46.3%) did not have GPFA in their EEGs.

EEG: Electroencephalogram; GPFA: Generalised paroxysmal fast activity; LGS: Lennox-Gastaut Syndrome; SSW: slow spike-and-waves

Asadi-Pooya AA. J Clin Neurosci. 2023;115:43-46.

Seizures in LGS

- Tonic seizures: They are brief (2-10 sec), more frequent in sleep (not in REM). May cause falls in wakefulness.
- Atypical absence: Clouding of consciousness with gradual onset and termination, sometimes with change in tone.
- Atonic seizures: The most common cause of falls.
- Myoclonic jerks: May cause falls.
- GTCSs
- Focal seizures
- Convulsive and non-convulsive status epilepticus

GTCS: Generalised Tonic-Clonic Seizure; LGS: Lennox-Gastaut Syndrome; REM: rapid eye movement

Asadi-Pooya AA. Neurol Sci. 2018;39(3):403-414.

It is not a prerequisite for LGS diagnosis (not seen in 7–10% at the beginning of the illness), but in long-term follow-up, it will happen almost in all.

Asadi-Pooya AA. Neurol Sci. 2018;39(3):403-414.

Cognitive and Behavioural Abnormalities

Interictal EEG in LGS

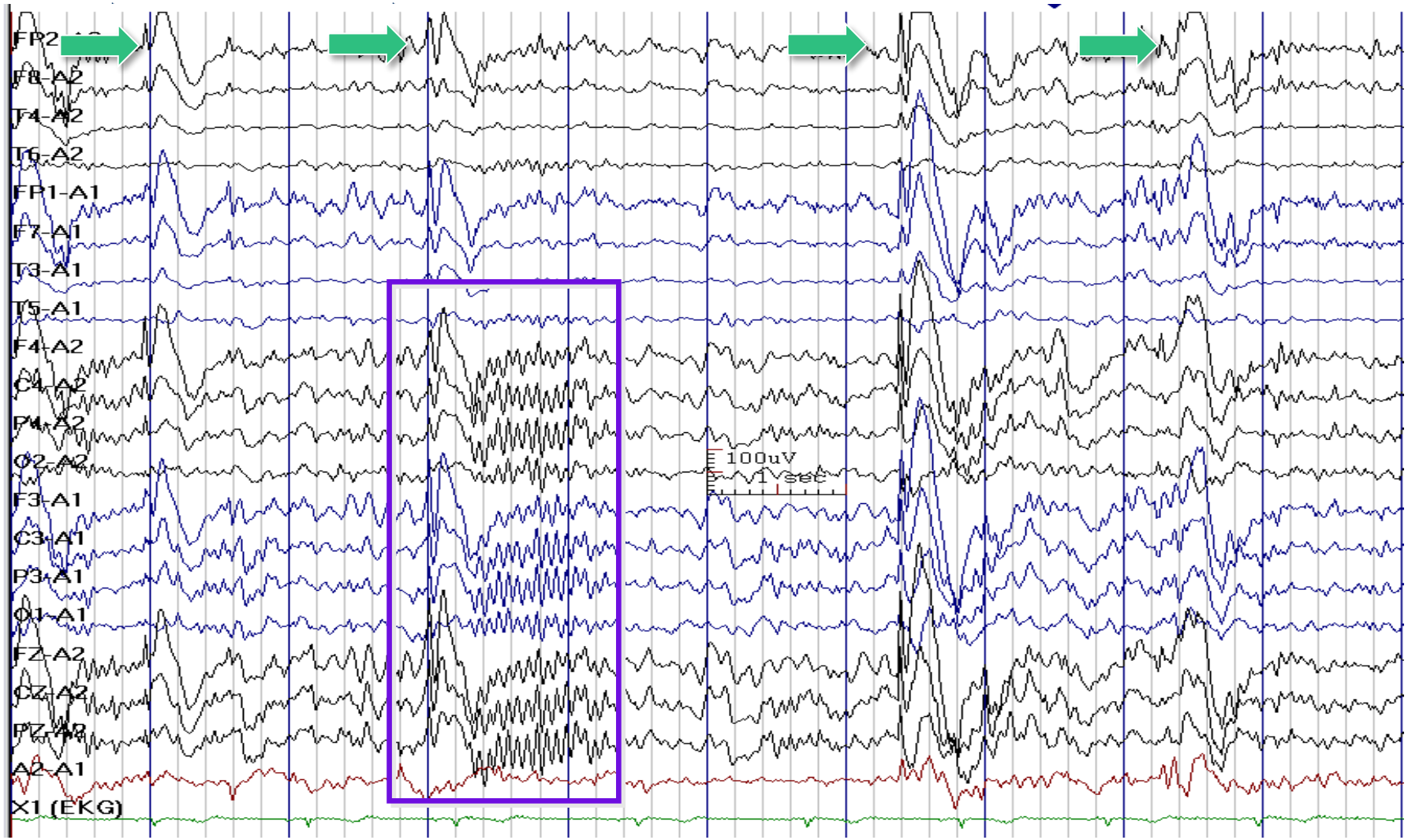
- Diffuse abnormalities of the background (slowing in wakefulness and abnormal sleep architecture): almost in all cases from the onset of seizures
- Slow (< 2.5 Hz) spike-and-waves (SSW): may take months to appear
- Generalised paroxysmal fast activity (GPFA): mainly in NREM sleep, if longer than 6 sec, usually produces a tonic seizure
- Focal or multifocal epileptiform discharges may be seen

EEG: Electroencephalogram; GPFA: Generalised paroxysmal fast activity; LGS: Lennox-Gastaut Syndrome; SSW: slow spike-and-waves

Asadi-Pooya AA. Neurol Sci. 2018;39(3):403-414.

Clinical Case: 10-year-old Female with LGS

SSW: slow spike-and-waves (green arrows)

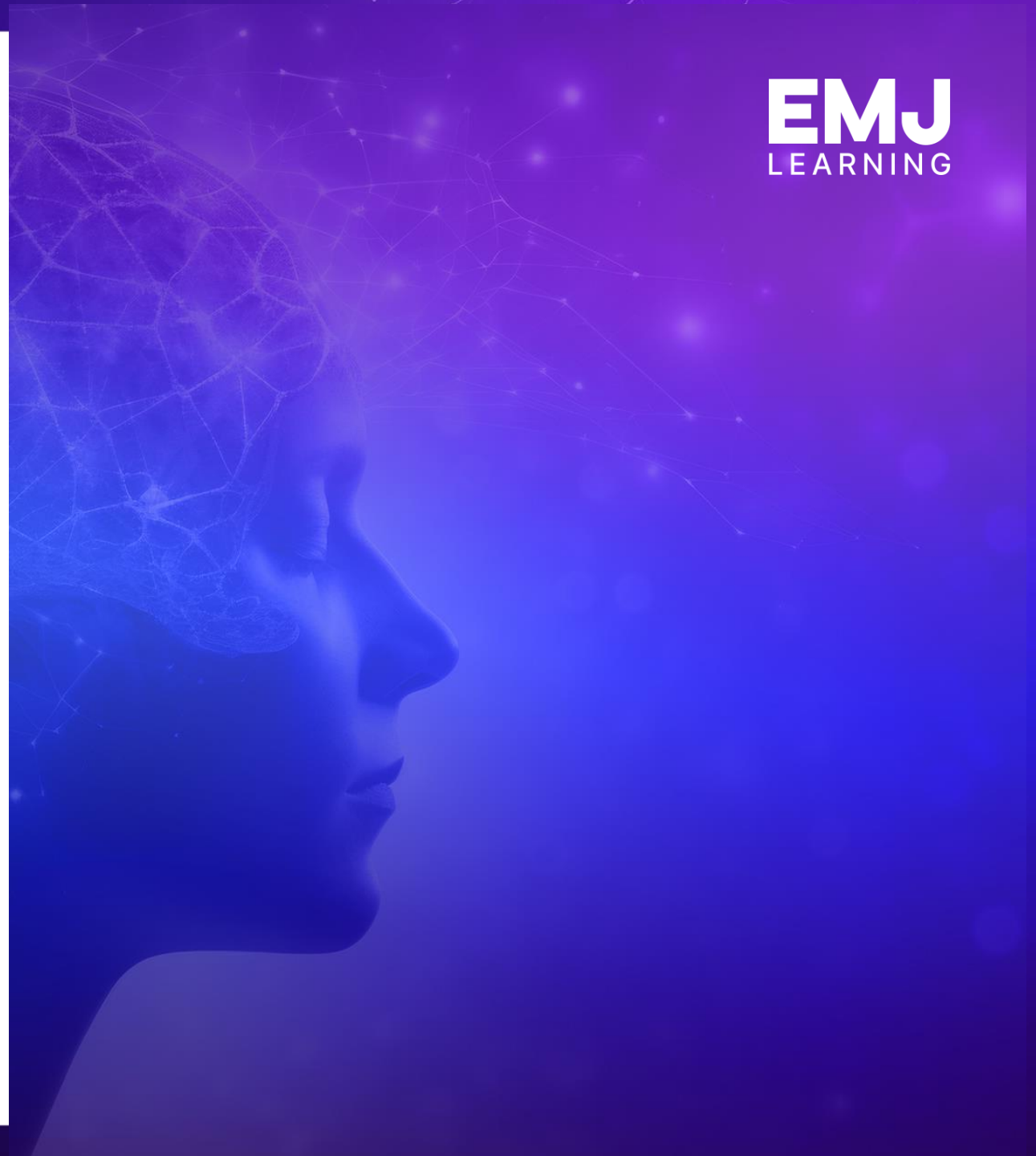


GPFA: Generalised paroxysmal fast activity (purple box)

Asadi-Pooya AA et al. Epileptic Disord. 2017;19(3):384.

Ictal EEG in LGS

- Tonic seizures: The EEG correlate of tonic seizure is GPFA
- Atypical absence: SSW is more regular, widely distributed and of longer duration than interictal SSW

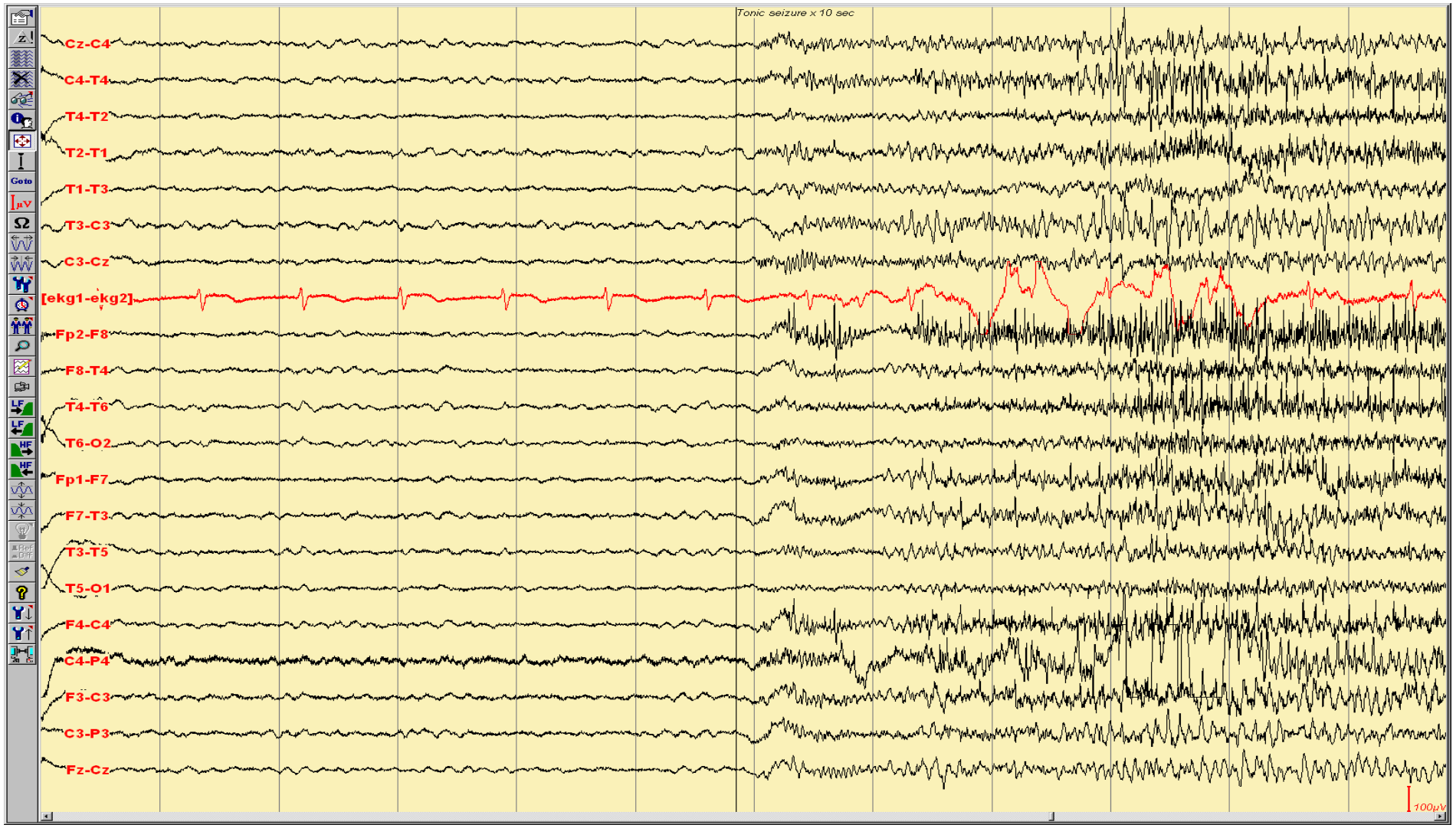


Asadi-Pooya AA. Neurol Sci. 2018;39(3):403-414.

GPFA: Generalised paroxysmal fast activity; SSW: slow spike-and-waves

Clinical Case: 10-year-old Male with LGS

Tonic seizure with GPFA



GPFA: generalised paroxysmal fast activity

Image provided from Asadi-Pooya patient archive with authorisation.

Diagnosis Pitfalls

- Not all patients have **all** of the core seizure types (i.e., tonic, atonic, and atypical absences), especially at the onset.
- The interictal EEG pattern, that is associated with LGS, is not pathognomonic to the disorder
- Therefore, we may start with a general epilepsy diagnosis to a nuanced consideration of a patient as LGS during a long-term follow-up

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EEG: Electroencephalogram; LGS: Lennox-Gastaut Syndrome

Epidemiology (Based of Traditional Definition)

- The prevalence of LGS is estimated between 1 and 2% of all patients with epilepsy and between 1 and 10% of childhood epilepsies
- LGS may evolve from another severe infantile epilepsy syndrome or aetiology, with approximately 20% of cases evolving from infantile epileptic spasms syndrome
- LGS usually begins between 18 months and 8 years of age, with a peak age at onset of 3–5 years. Onset in the second decade is not common
- LGS persists into adulthood in nearly all cases, and seizures remain drug-resistant

LGS: Lennox-Gastaut Syndrome

Asadi-Pooya AA. Neurol Sci. 2018;39(3):403-414.

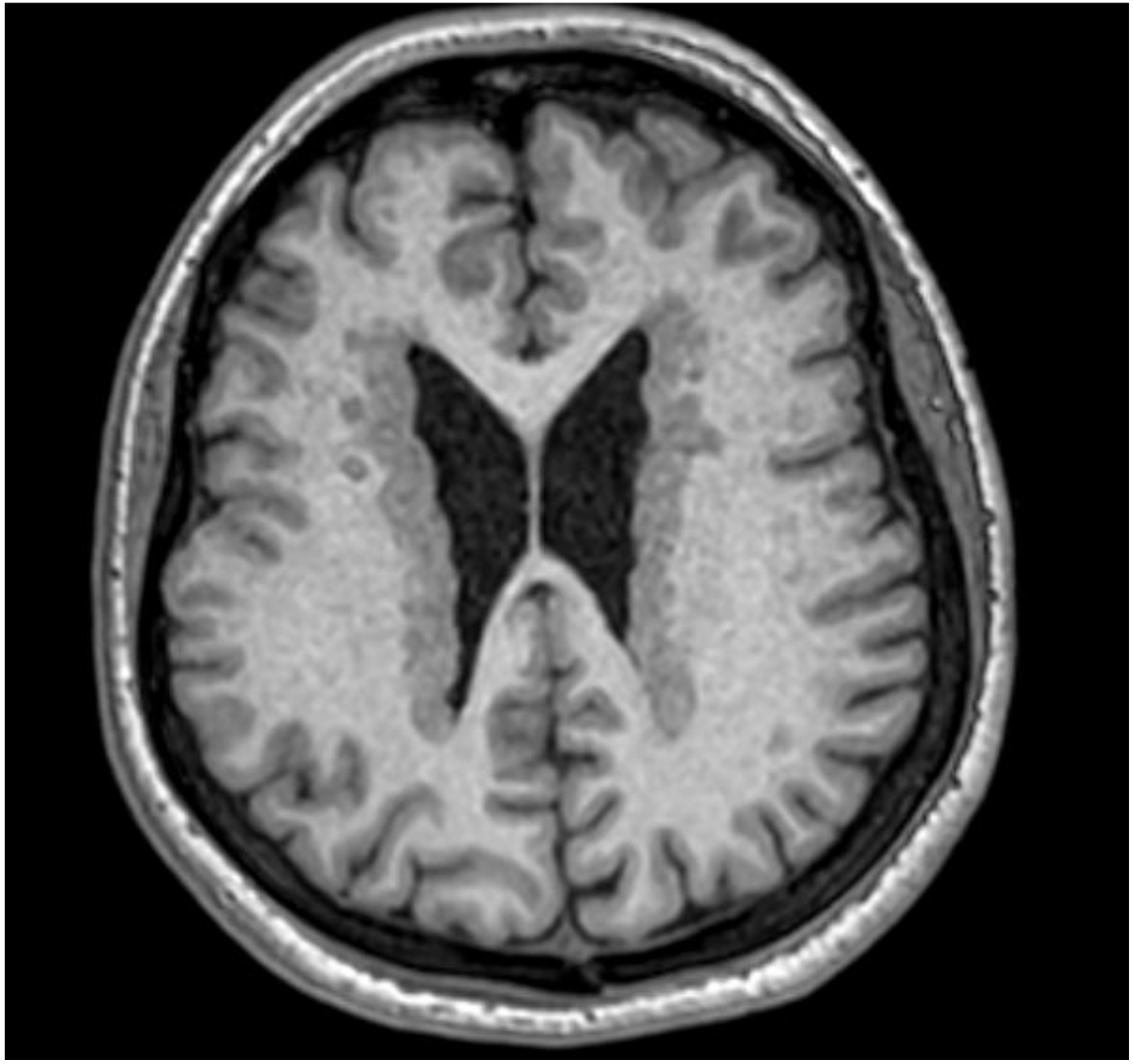
Aetiology

Identifiable [Symptomatic (structural-metabolic-genetic)]:

- Brain malformations
- Hypoxic ischemic encephalopathy
- Infections
- Tuberous sclerosis complex
- Genetic diseases
- Metabolic diseases

Unknown (Cryptogenic): X% of cases. Normal imaging, no identified aetiology (it depends on the resources)

Asadi-Pooya AA. Neurol Sci. 2018;39(3):403-414.



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Brain Imaging

As structural causes are the most common aetiology, brain MRI is strongly recommended

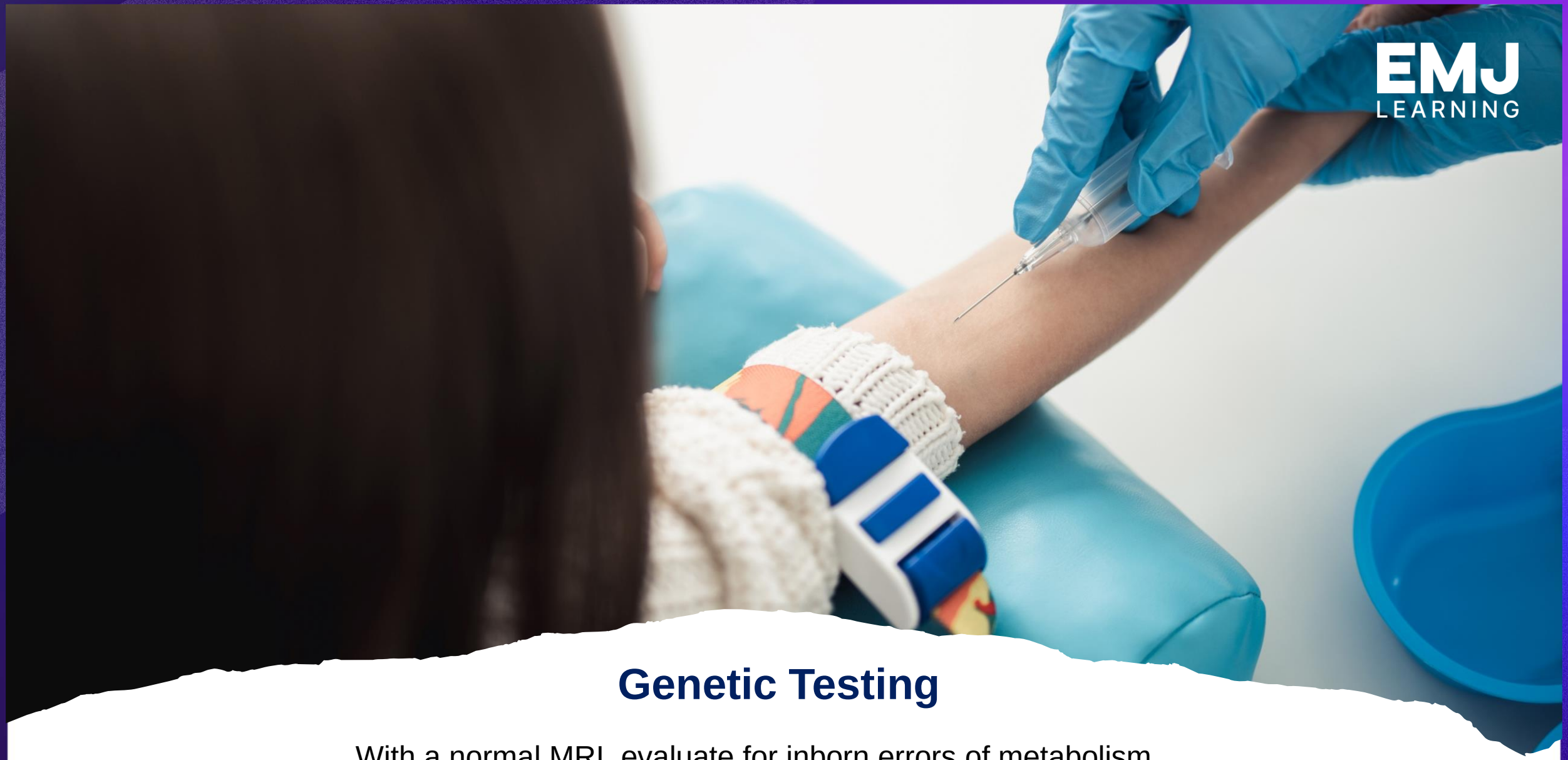
Image provided from Asadi-Pooya patient archive with authorisation.

MRI: Magnetic resonance imaging

Genetic Testing

- **Whole exome sequencing** or an epilepsy gene panel, particularly if no aetiology is found after clinical examination and MRI
- Genetic testing should also be considered for patients with structural brain disorders suggestive of an underlying genetic cause
- Copy number variants, SCN1A mutations, CHD2 mutations, de novo missense mutation in the forkhead box G1 (FOXG1) gene, and mutations in dynamin 1 (DNM1)

MRI: Magnetic resonance imaging



Genetic Testing

With a normal MRI, evaluate for inborn errors of metabolism.

MRI: Magnetic resonance imaging

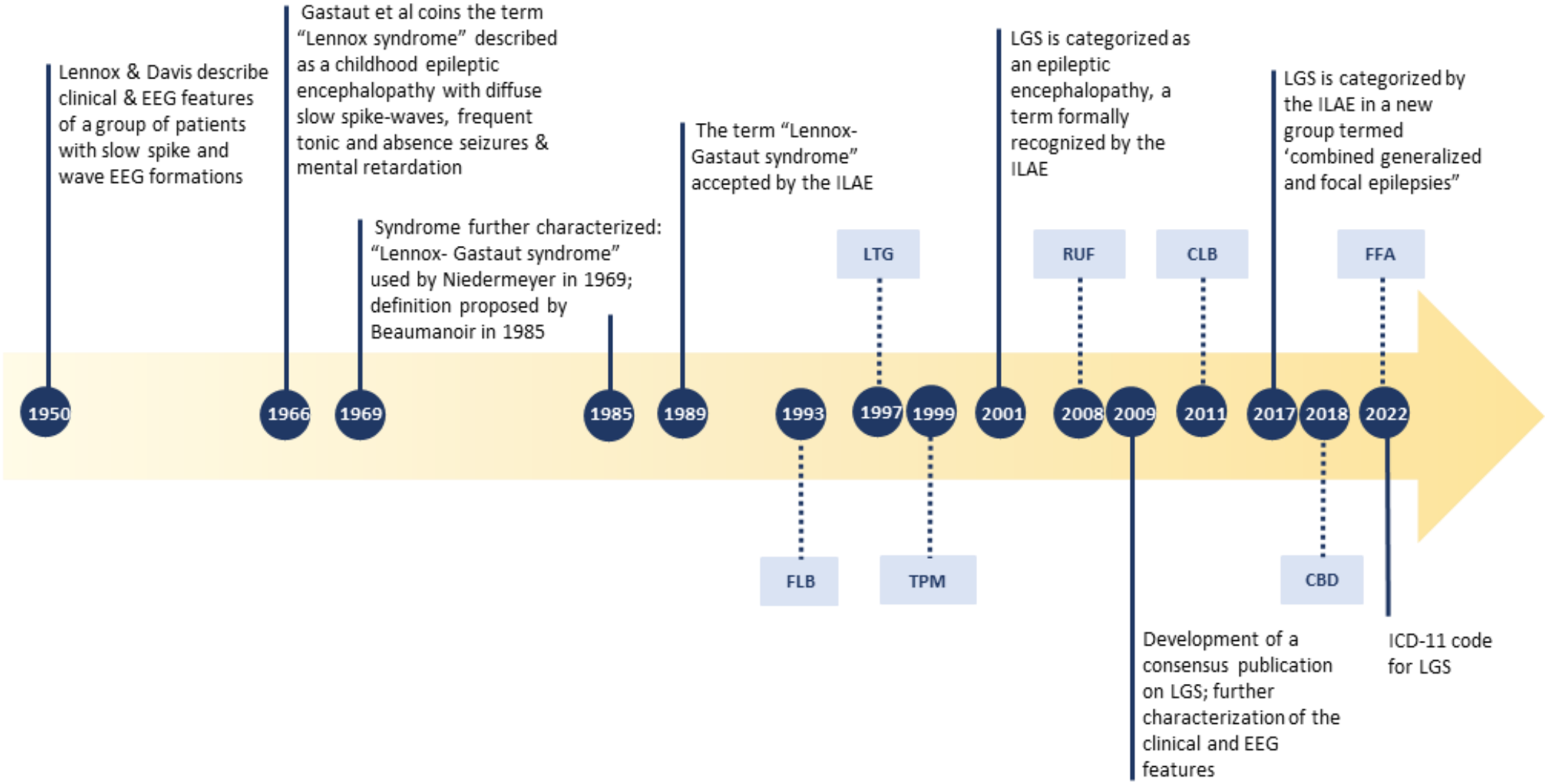
The Treatment Landscape Lennox-Gastaut syndrome

Adam Strzelczyk, MD, MHBA, FEAN

Professor/ Consultant Neurologist

Goethe-University Frankfurt, Germany

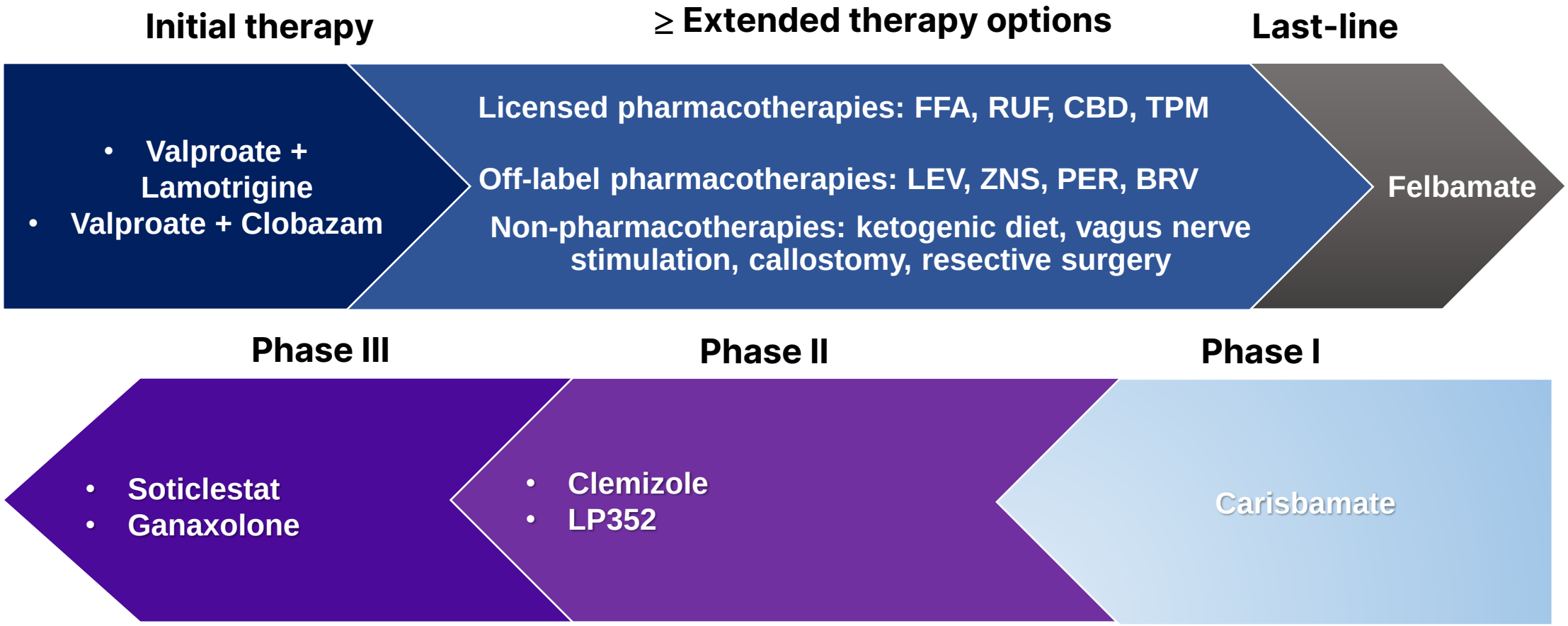
History of the Characterisation and Treatment of LGS



CBD: cannabidiol; CLB: clobazam; FFA: fenfluramine; FLB: felbamate; LTG: lamotrigine; RUF: rufinamide; TPM: topiramate

Strzelczyk et al. Orphanet J Rare Dis. 2023;18(1):42.

History of the Characterisation and Treatment of LGS



BRV: brivaracetam; CBD: cannabidiol; FFA: fenfluramine; LEV: levetiracetam; PER: perampanel; RUF: rufinamide; TPM: topiramate; ZNS: zonisamide

Modified from Strzelczyk A, Schubert-Bast S. CNS Drugs 2021

Psycho-behavioural and Cognitive Adverse Events of ASMs in DEE

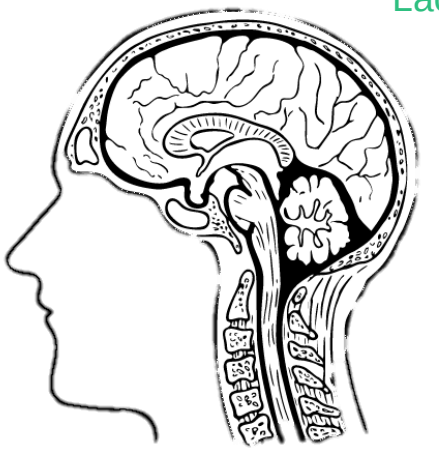
DEE	Classification of evidence		Caution
	Class I-II	Class III-IV	
DS	Valproate Topiramate Stiripentol* Clobazam Cannabidiol* Fenfluramine*	Bromide Levetiracetam Zonisamide Ethosuximide Perampanel Brivaracetam	Predominant sodium channel blockers Gabapentinoids Tiagabine Vigabatrin
LGS	Valproate Topiramate* Lamotrigine* Rufinamide* Clobazam* Cannabidiol* Fenfluramine*	Felbamate* Levetiracetam Zonisamide Ethosuximide Perampanel Brivaracetam	Carbamazepine Oxcarbazepine Gabapentinoids Phenytoin
Notes	*Carries approved indication for specified condition		

For specific product information please consult your local prescribing information.

ASM: anti-seizure medications; DEE: developmental and epileptic encephalopathy; DS: Dravet syndrome; LGS: Lennox-Gastaut Syndrome

Strzelczyk A, Schubert-Bast S. CNS Drugs. 2022;36(10):1079-1111. Wirrell EC et al. Epilepsia. 2022;63(7):1761-1777. Strzelczyk A, Schubert-Bast S. CNS Drugs. 2022;36:217–237. Northrup H et al. Pediatr Neurol. 2021;123:50-66. Montouris G et al. Epilepsy Behav. 2020;110:107146. Strzelczyk A, Schubert-Bast S. CNS Drugs. 2021;35(1):61-83.

Psycho-behavioural and Cognitive Adverse Events of ASMs



Mood/ Psychiatric

Topiramate
Levetiracetam
Brivaracetam
Zonisamide
Perampanel
Vigabatrine
Bromide

Valproate
Rufinamide
Lamotrigine
Cannabidiol

Cognition

Tupiramate
Zonisamide

Cannabidiol
Fenfluramine
Levetiracetam(?)
Brivaracetam(?)
Lamotrigine
Vigabatrine (in TSC)
Rufinamide
Lacosamide

Behaviour

Topiramate
Levetiracetam
Zonisamide
Perampanel
Bromide
Brivaracetam
Stiripentol

Lamotrigine

Sedation

All ASMs, especially with up-titration

Sleep

Lamotrigine

Cannabidiol(?)
Perampanel
Pregabalin
Clobazam

Treatment with ASMs may have negative, positive, or neutral effects on the cognitive, behavioural, psychiatric, and sleep impairments that are common in patients with DEEs

For specific product information please consult your local prescribing information.

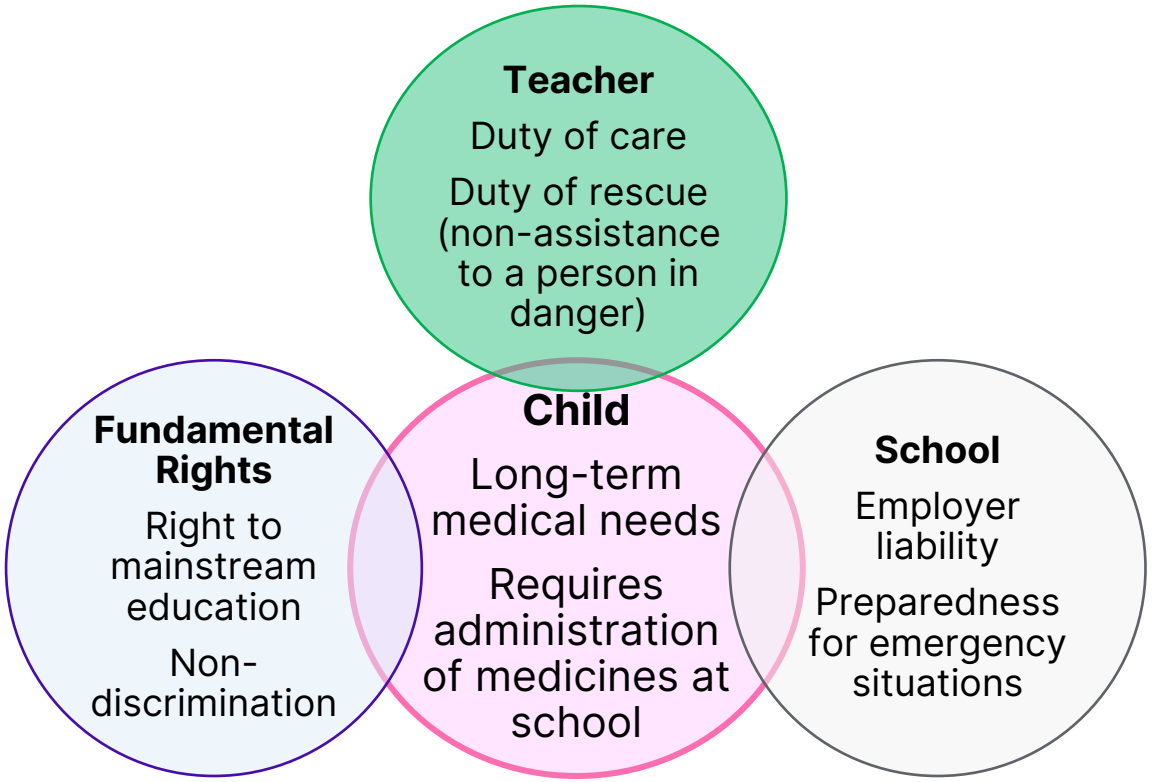
ASM: anti-seizure medications; DEE: developmental and epileptic encephalopathies; TSC: tuberous sclerosis complex

Strzelczyk A, Schubert-Bast S. CNS Drugs. 2022;36(10):1079-1111

Seizure Emergency Plan

- Familiarise with one product
- Show how to apply: training of parents, caregivers
- Explain basics about normal protective actions during a seizure
- Explain when to give the rescue medication
  - Acute (convulsive) seizure lasting longer than 2-5 minutes
- If no success within 5-10 minutes, explain when to call emergency service
- Discuss who else can give the rescue medication
  - Teacher(s), Grandparent(s), other Layperson(s)

Seizure Emergency Plan



Legal frameworks converging in the situation of children requiring epilepsy rescue medication at school.

- Patients who already suffered from a prolonged seizure/status epilepticus
- Developmental and epileptic encephalopathies
  - Dravet, LGS, TSC ...
- Epilepsies with seizure clusters
- Patients at risk for non-compliance ASMs (or discontinuation)

ASM: anti-seizure medications; LGS: Lennox-Gastaut Syndrome; TSC: tuberous sclerosis complex

Wait S et al. Eur J Paediatr Neurol. 2013; 17(1):14-23.

Rescue medication to children with prolonged acute convulsive seizures: What happens in community practice?

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Main issues that arise in the implementation of existing guidance on the administration of medication in schools.

- Low awareness and understanding of epilepsy and PCS in schools
- Guidance is outdated and carries little weight in practice
- Legal frameworks are vague, thus specific applications to rescue medication are open to interpretation
- Teachers and school staff have no legal obligation to administer rescue medication to children
- Schools and teachers fear liability in case of injury to a child who receives rescue medication under their care
- Training requirements for school staff on the administration of medicines are often unclear
- Unclear information is provided to parents
- There is poor integration between health and educational services
- There is a lack of a cohesive framework across the entire educational system (inspection, school doctor/nurses, training,...)

PCS: prolonged acute convulsive seizures

Wait S et al. Eur J Paediatr Neurol. 2013; 17(1):14-23.

SEIZURE ACTION PLAN (SAP)

EPILEPSY FOUNDATION

Name: _____ Birth Date: _____

Address: _____ Phone: _____

Emergency Contact/Relationship: _____ Phone: _____

Seizure Information

Seizure Type	How Long It Lasts	How Often	What Happens

How to respond to a seizure (check all that apply)

- ☐ First aid – **Stay. Safe. Side.**
- ☐ Give rescue therapy according to SAP
- ☐ Notify emergency contact
- ☐ Notify emergency contact at _____
- ☐ Call 911 for transport to _____
- ☐ Other _____

First Aid for any seizure

- ☐ **STAY** calm, keep calm, begin timing seizure
- ☐ Keep me **SAFE** – remove harmful objects, don't restrain, protect head
- ☐ **SIDE** – turn on side if not awake, keep airway clear, don't put objects in mouth
- ☐ **STAY** until recovered from seizure
- ☐ Swipe magnet for VNS
- ☐ Write down what happens _____
- ☐ Other _____

When to call 911

- ☐ Seizure with loss of consciousness longer than 5 minutes, not responding to rescue med if available
- ☐ Repeated seizures longer than 10 minutes, no recovery between them, not responding to rescue med if available
- ☐ Difficulty breathing after seizure
- ☐ Serious injury occurs or suspected, seizure in water

When to call your provider first

- ☐ Change in seizure type, number or pattern
- ☐ Person does not return to usual behavior (i.e., confused for a long period)
- ☐ First time seizure that stops on its' own
- ☐ Other medical problems or pregnancy need to be checked

When **rescue therapy** may be needed:

When and What to do

If seizure (cluster, # or length) _____

Name of Med/Rx _____ How much to give (dose) _____

How to give _____

If seizure (cluster, # or length) _____

Name of Med/Rx _____ How much to give (dose) _____

How to give _____

If seizure (cluster, # or length) _____

Name of Med/Rx _____ How much to give (dose) _____

How to give _____

Care after seizure

What type of help is needed? (describe) _____

When is person able to resume usual activity? _____

Special instructions

First Responders: _____

Emergency Department: _____

Daily seizure medicine

Medicine Name	Total Daily Amount	Amount of Tab/Liquid	How Taken (time of each dose and how much)

Other information

Triggers: _____

Important Medical History: _____

Allergies: _____

Epilepsy Surgery (type, date, side effects) _____

Device: ☐ VNS ☐ RNS ☐ DBS Date Implanted _____

Diet Therapy: ☐ Ketogenic ☐ Low Glycemic ☐ Modified Atkins ☐ Other (describe) _____

Special Instructions: _____

Health care contacts

Epilepsy Provider: _____ Phone: _____

Primary Care: _____ Phone: _____

Preferred Hospital: _____ Phone: _____

Pharmacy: _____ Phone: _____

My signature: _____ Date _____

Provider Signature: _____ Date: _____

epilepsy.com
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EPILEPSY FOUNDATION

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Available from: https://www.epilepsy.com

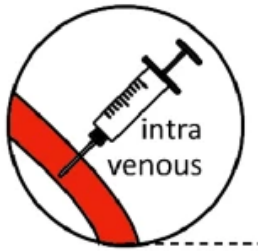
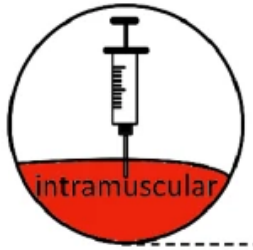
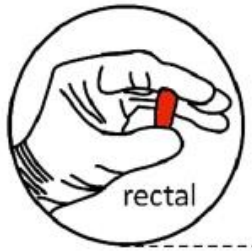
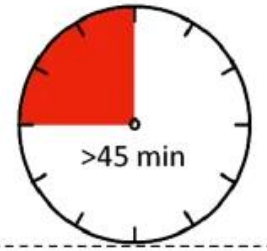
How to Implement a Seizure Emergency Plan?

Keys to Development
• Customised • Clear • User-friendly • Step-by-step instructions • Practical to use

Keys to Implementation			
Standardisation of form and location in the electronic medical records	**Education** of HCPs, patients, and caregivers	**Access** when needed for immediate use	**Reviewing and Updating** when a change is made and on a regular basis

Patel AD, Becker DA. Epilepsia, 2022; 63 (Suppl1):S25-S33

Use of Rescue Medication

Route of delivery	Available benzodiazepines#	Time till cessation	Comment on clinical use in status epilepticus
	• Clonazepam • Diazepam • Lorazepam • Midazolam		• Gold standard if PVC established • Restricted to medical professionals
	• Diazepam • Lorazepam • Midazolam		• Feasible option if PVC is not yet established • Easy to use for medical non-professionals
	• Diazepam • Lorazepam • Midazolam		• Feasible option if PVC is not yet established • Autoinjectors available for non-professionals
	• Lorazepam • Midazolam		• Feasible option for seizure clusters or in palliative care settings • Easy to use for medical non-professionals
	• Diazepam		• Feasible option for seizure clusters or in palliative care settings • Difficult to handle, may cause discomfort
	• Clonazepam • Diazepam • Lorazepam • Midazolam		• Inadequate route for treatment of status epilepticus

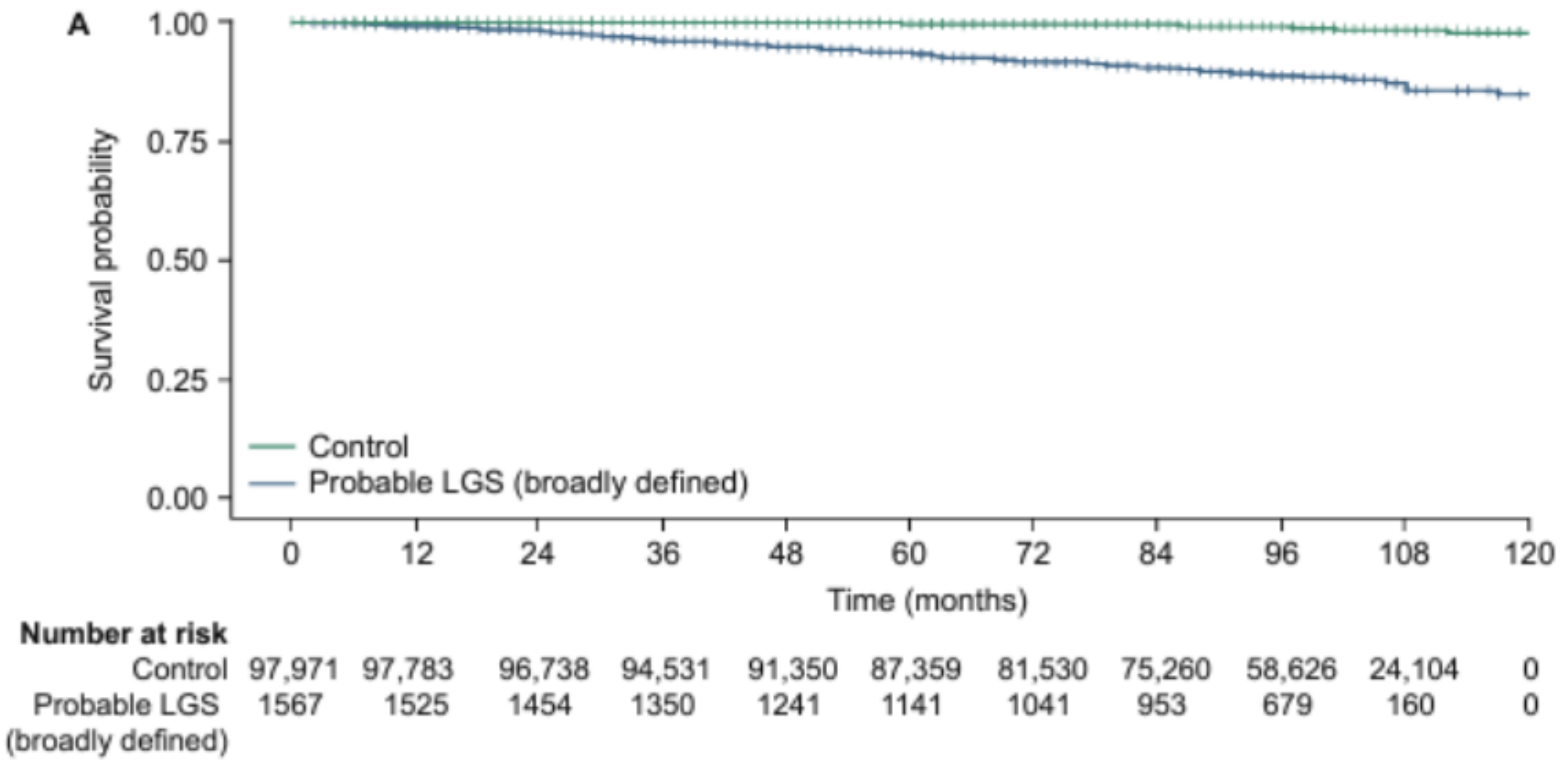
*contributed equally; #availability may differ depending on country

i.m.: intramuscular; i.n.: intranasal; i.v.: intravenous; PVC: peripheral vein catheter

Kienitz et al. CNS Drugs. 2022;36(9):951-975.

Epidemiology, Healthcare Resource Use, and Mortality In LGS

Mortality in Lennox-Gastaut Syndrome

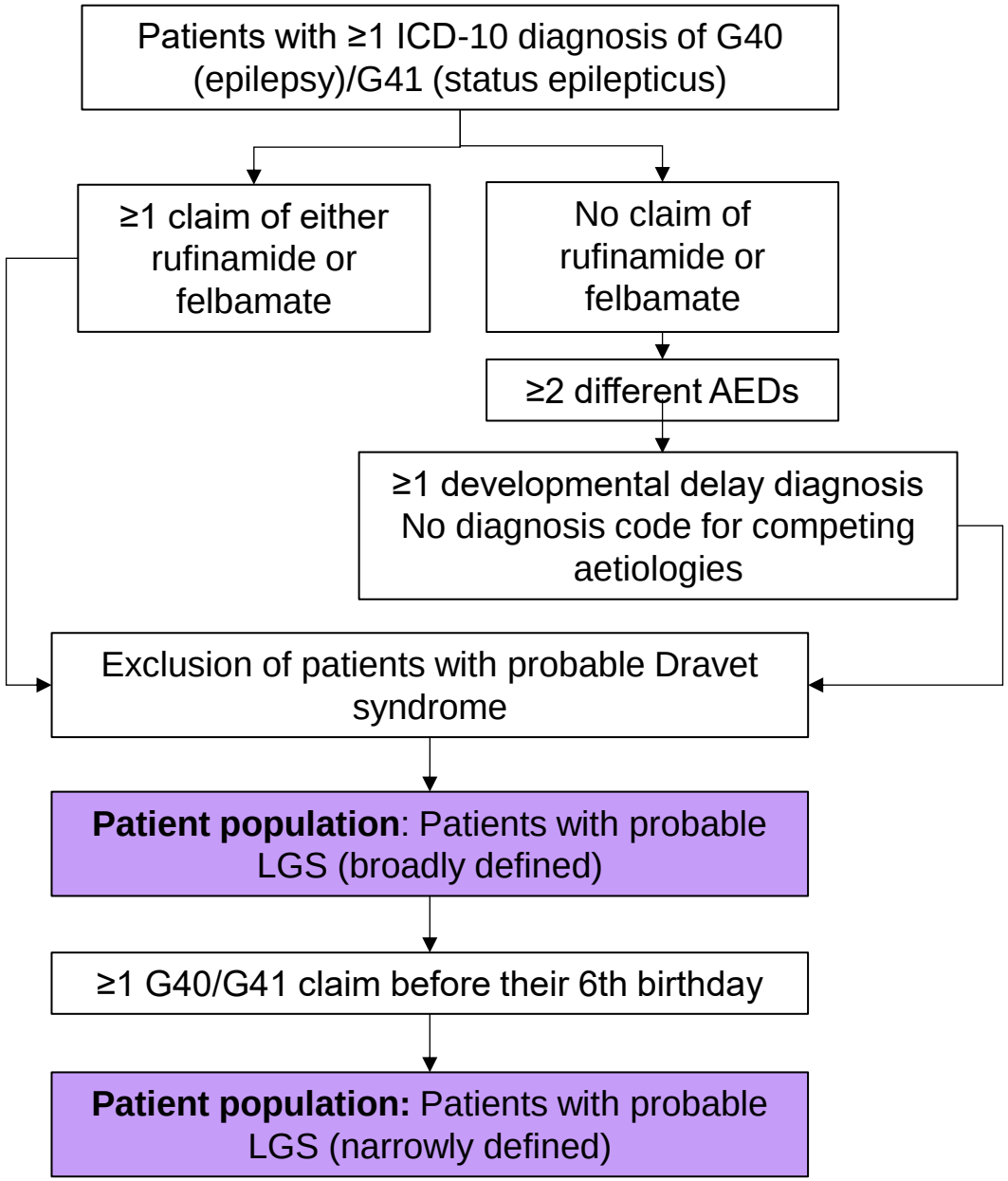


UK: crude mortality rates of 6.12 (confirmed LGS) and 4.17 (probable LGS) deaths per 1000 person-years (Chin et al. Seizure 2021; 91:159-166).

Germany: mortality rate between 2.9% to 10% depending on definition (Strzelczyk et al. Epilepsia. 2021;62(10):2518-2527).

From: Strzelczyk et al. Epilepsy Behav. 2021:115:107647.

Patient Selection Process for Probable LGS



AED: anti-epileptic drug; DS: ICD-10: International Classification of Diseases, 10th Revision; LGS: Lennox-Gastaut syndrome

Strzelczyk A et al. Epilepsy Behav. 2021:115:107647.

Summary of Cost Data

	All patients	Years where patients prescribed with rescue medication	Years where patients not prescribed with rescue medication
Annual cost per patient-year, € Patient-years	**1379**	**618**	**761**
Total			
Mean	22,787	33,872	13,785
Median (Q1–Q3)	4439 (0–18,489)	11,897 (0–30,500)	2058 (0–9120)
Inpatient			
Mean	7422	9776	5511
Median (Q1–Q3)	0 (0–5394)	1427 (0–10,628)	0 (0–1947)
Epilepsy-related			
Mean	5636	8336	3288
Median (Q1–Q3)	0 (0–5243)	2580 (0–8814)	0 (0–2008)
Outpatient			
Mean	1390	1826	1036
Median (Q1–Q3)	708 (0–1681)	1122 (0–2005)	388 (0–1336)
Medication			
Mean	2243	3479	1240
Median (Q1–Q3)	427 (0–1991)	1126 (0–3797)	146 (0–971)
AEDs			
Mean	309	483	169
Median (Q1–Q3)	100 (0–354)	225 (17–576)	0 (0–196)

Rescue medication use is defined by having one prescription of midazolam, diazepam (rectal formulation), or chloralhydrate.

AED: anti-epileptic drug; LGS: Lennox-Gastaut syndrome; Q1–Q3: interquartile range; SD: standard deviation.

Strzelczyk A et al. Epilepsy Behav. 2021:115:107647.

Patients with LGS are a Vulnerable Population

- Important to know the underlying course of epilepsy

- Children, Adults, and Elderly with LGS
  - Epilepsy acquired during early childhood
  - Comorbidities are developed and increase over time
  - ASM rarely stop all seizures and may no longer be tolerated or lose efficacy

- Children, Adults, and Elderly severely depend on caregivers
  - Mothers and families are primary caregivers
  - Medical information might get lost at transition
  - Care might be transitioned to institutions or other relatives

ASM: anti-seizure medications

Patients with LGS are a Vulnerable Population

- Know your patients and their needs (changing over time)

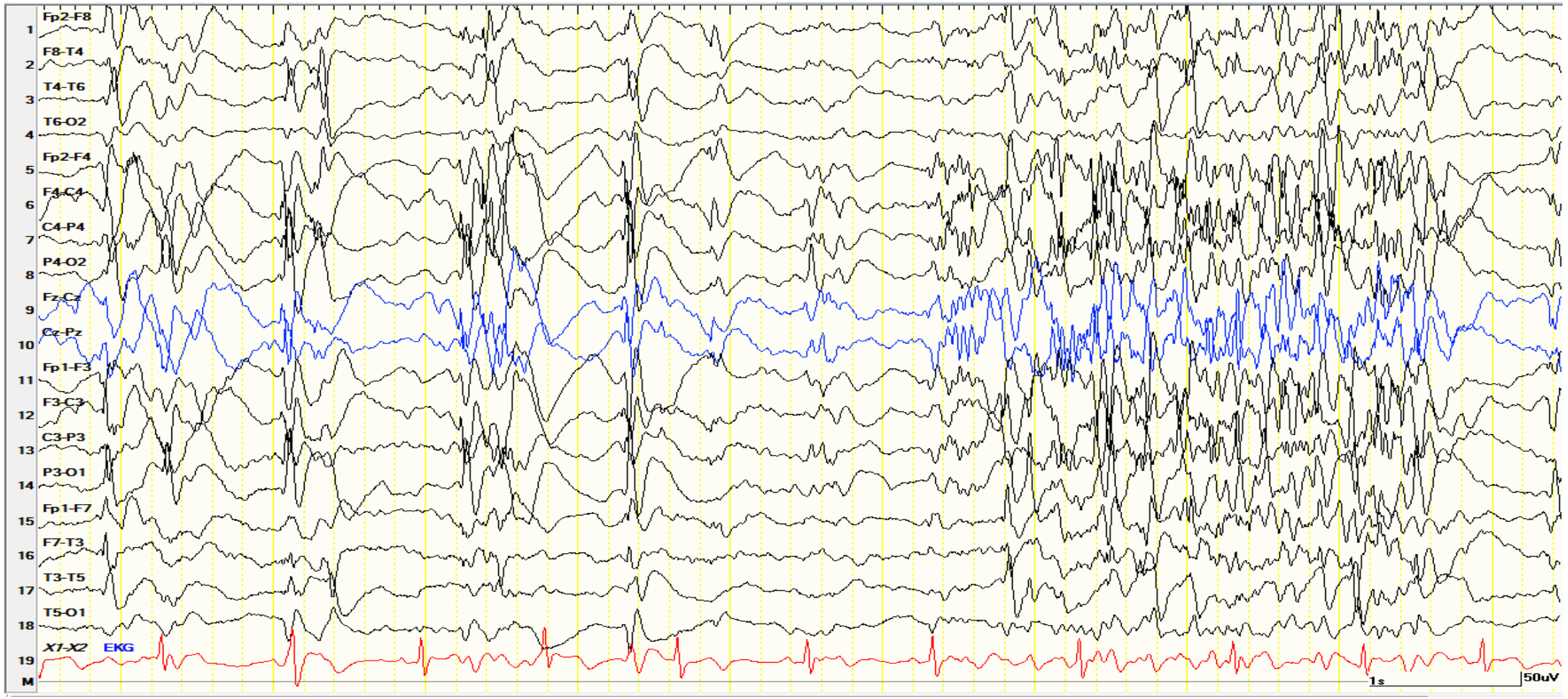
- Children, Adults, and Elderly with LGS
  - High direct and indirect costs
  - Comorbidities will influence outcome
  - Different tolerability profiles of ASMs
  - Genetic results do influence outcome

- Children, Adults, and Elderly severely depend on caregivers
  - LGS with high indirect costs for caregivers
  - Low QoL in patients and caregivers

- High mortality in LGS and other DEEs

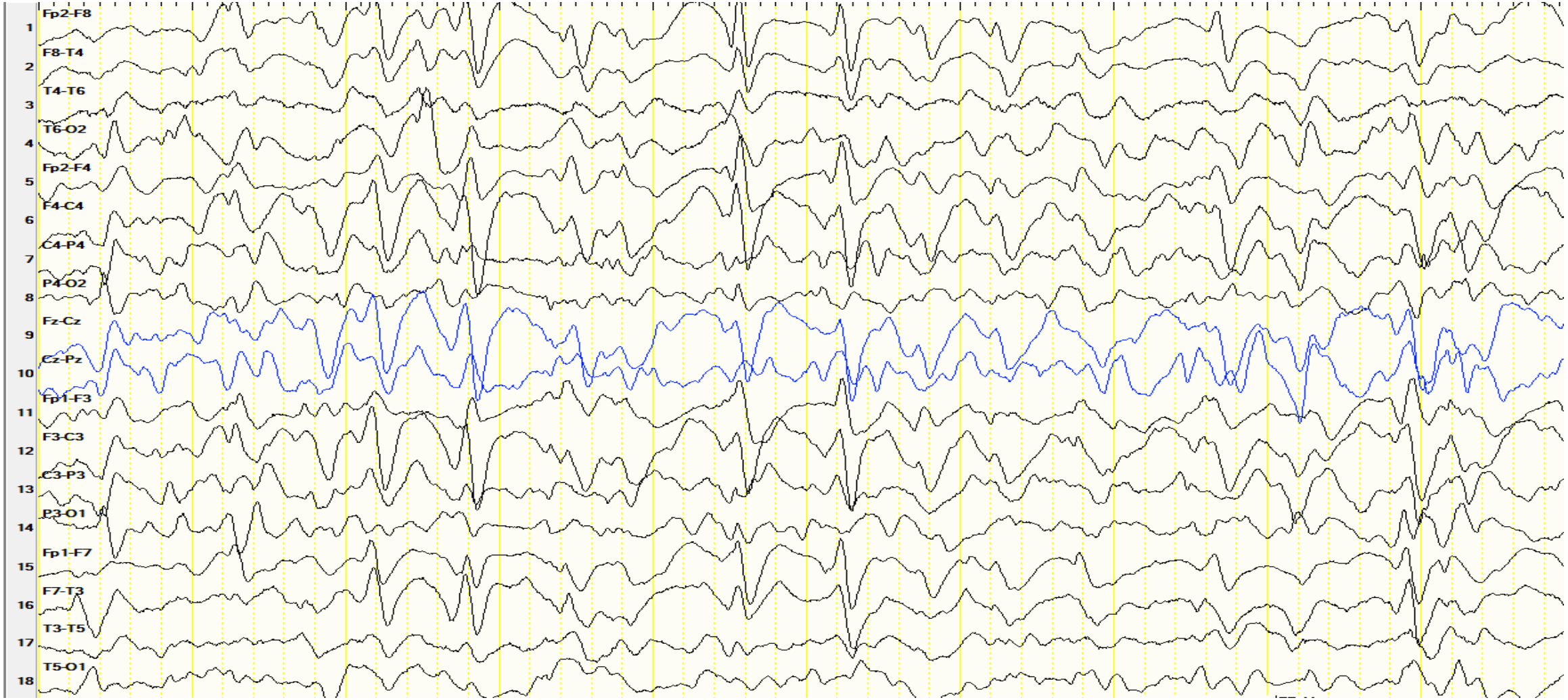
ASM: anti-seizure medications; DEE: developmental and epileptic encephalopathy; QoL: quality of life; LGS: Lennox-Gastaut syndrome

EEG in LGS: Triad of Symptoms



Strzelczyk A, Schubert-Bast S. CNS Drugs 2021

EEG in LGS: Triad of Symptoms



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EEG in LGS: Triad of Symptoms

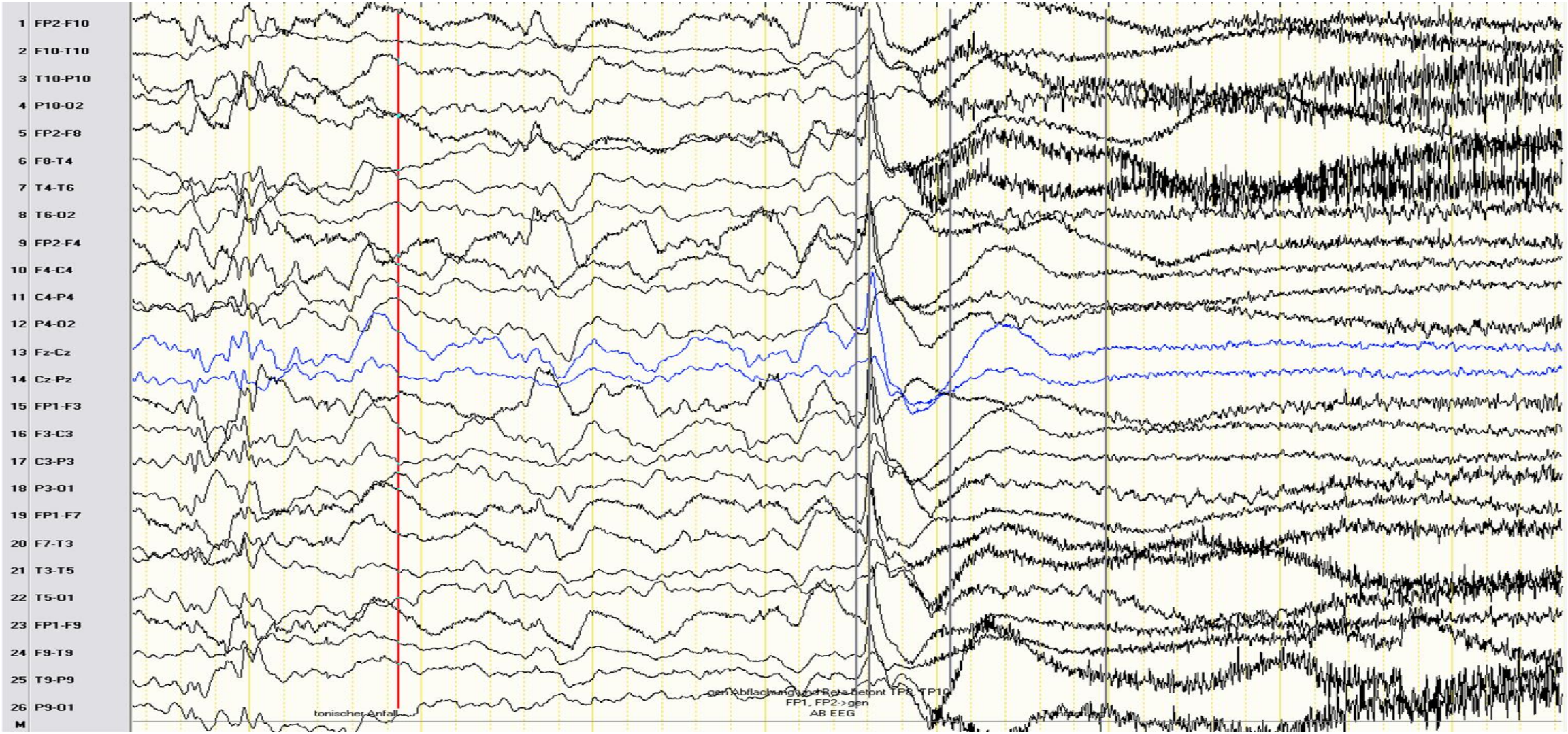

Image provided from Strzelczyk patient archive with authorisation.

Applying Perspectives and Practical Approaches

Implementing the ILAE Definition and Diagnostic Criteria of LGS

Experience of Treatment Pathways for LGS

Treatment Approaches for Behavioural Abnormalities

Options for Resource-Poor Countries

Take Home Messages

Thank you for Watching

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